Does urinary neutrophil gelatinase-associated lipocalin really solve the issue of discriminating prerenal from intrinsic acute kidney injury?

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To the Editor: Singer *et al.*[1] reported on the diagnostic value of urinary neutrophil gelatinase-associated lipocalin (uNGAL) in the discrimination of intrinsic and prerenal acute kidney injury (AKI), concluding that uNGAL significantly improves diagnostic capacity. For several reasons, we feel that this conclusion might be overoptimistic.

First, a biomarker would be most valuable when there is doubt about the correct diagnosis of intrinsic vs. prerenal AKI. Currently, this differential diagnosis is made on the basis of patient history, volume status, the use of nephrotoxic medications, and so on; using this approach as the gold standard, no clear differential diagnosis could be made in a substantial number of cases (38 out of 145); however, in this group, uNGAL was not able to make a discrimination as well. Thus, uNGAL is not helping in the discrimination in those patients in whom it would be most needed. Second, the diagnostic accuracy of the multivariate model increases only modestly from 68.3 to 74.5 % when uNGAL is added. It would have been interesting to see the effect of inclusion of other parameters, such as urinary volume or evolution of serum creatinine in the first 4 h of admission.

Third, the authors use a composite end point, including factors with a substantially different impact: mortality was put at the same level as renal replacement therapy and step-up of RIFLE class.

Fourth, authors use RIFLE rather than the Acute Kidney Injury Network classification.[2] In contrast to the former, the latter requires that patients be volume-repleted. If the authors[1] would have applied this strategy, they would probably already have distinguished the majority of the prerenal cases, as is obvious from Figure 2, in which it can clearly be seen that serum creatinine is decreasing in the prerenal subjects. Furthermore, the additional discriminatory value of uNGAL would be less than that presented in the current analysis.

In conclusion, we believe that the paper by Singer *et al*[1] does not change the message that the diagnostic value of uNGAL is overoptimistic.[3] Advocating the use of uNGAL might lead to neglecting other important clinical criteria.

1. Singer E, Elger A, Elitok S *et al.* Urinary neutrophil gelatinase-associated lipocalin distinguishes pre-renal from intrinsic renal failure and predicts outcomes. *Kidney Int* 2011; **80**: 405–414.
2. Mehta RL, Kellum JA, Shah SV *et al.* Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; **11**: R31.
3. Lameire N, Vanholder R, Van Biesen W. How to use biomarkers efficiently in acute kidney injury. *Kidney Int* 2011; **79**: 1047–1050.

The Authors Reply: We thank Drs Van Biesen *et al.*[1] for their letter regarding our study where they question the diagnostic utility of determining urinary neutrophil gelatinase-associated lipocalin (uNGAL) in patients that present with elevated serum creatinine. Among physicians, nephrologists are particularly aware that the disease phenotype is critically time-dependent as patients can be, e.g., in positive sodium balance without edema, or in complete renal failure with 'normal' serum creatinine. In addition, decreases in glomerular filtration rate are part of the normal homeostatic response to marked reductions of extracellular fluid volume and also to the neurohumoral response triggered by diseases in which cardiovascular homeostasis is compromised, i.e., congestive heart failure, hypoalbuminemia, and so on. In all these conditions, serum creatinine can be elevated and whether this is due to an appropriate renal response to neurohumoral signals (i.e., prerenal) or to an intrinsic acute kidney injury (AKI) has vexed physicians and nephrologists for decades. Indeed, true distinctions of 'prerenal' vs. 'intrinsic renal' increases in plasma creatinine are only made retrospectively depending on the patient's response to therapy. Moreover, in rich societies 'prerenal' increases in plasma creatinine are most often due to abnormal cardiovascular function so that acute administration of volume is often not indicated. Given these complexities, development of a test that immediately assists the physician confronting a patient with an elevated serum creatinine would be highly valuable. Our study now adds to a growing body of evidence supporting the concept that NGAL correlates with processes that induce intrinsic AKI, but not with transient pre-renal elevations of creatinine.[2–4]

Specifically, Van Biesen *et al.*[1] suggested that a volume-repleted study population should have been selected, but this would have obscured our intention to test the prospective discriminatory ability of uNGAL. Furthermore, we would imagine that 4-h repeat measurements of urinary output and serum creatinine would be neither sensitive nor compatible with rapid triage. Moreover, similar to previous studies,[4,5] NGAL predicted poor clinical outcomes whether mortality was included into a composite outcome (our paper) or only renal-specific outcomes were considered (Table 1). Van Biesen *et al.*[1] are particularly concerned with the utility of uNGAL in patients who were unclassifiable. We point out that we aimed to make gold standard diagnoses of prerenal and intrinsic AKI,